Role of Antimicrobial Agents in the Management of Exacerbations of COPD

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Abstract

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are a common occurrence and characterize the natural history of the disease. Over the past decade, new knowledge has substantially enhanced our understanding of the pathogenesis, outcome and natural history of AECOPD. The exacerbations not only greatly reduce the quality of life of these patients, but also result in hospitalization, respiratory failure, and death. The exacerbations are the major cost drivers in consumption of healthcare resources by COPD patients. Although bacterial infections are the most common etiologic agents, the role of viruses in COPD exacerbations is being increasingly recognized. The efficacy of antimicrobial therapy in acute exacerbations has established a causative role for bacterial infections. Recent molecular typing of sputum isolates further supports the role of bacteria in AECOPD. Isolation of a new strain of *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae* was associated with a considerable risk of an exacerbation. Lower airway bacterial colonization in stable patients with COPD instigates airway inflammation, which leads to a protracted self-perpetuating vicious circle of progressive lung damage and disease progression. A significant proportion of patients treated for COPD exacerbation demonstrate incomplete recovery, and frequent exacerbations contribute to decline in lung function. The predictors of poor outcome include advanced age, significant impairment of lung function, poor performance status, comorbid conditions and history of previous frequent exacerbations requiring antibacterials or systemic corticosteroids. These high-risk patients, who are likely to harbor organisms resistant to commonly used antimicrobials, should be identified and treated with antimicrobials with a low potential for failure. An aggressive management approach in complicated exacerbations may reduce costs by reducing healthcare utilization and hospitalization.

First described by Badham in 1808 and then by Laennec in 1827, COPD is a devastating respiratory illness that affects a sizeable world population and is the fourth leading cause of death in US after heart disease, cancer and stroke.[1,2] Primarily a consequence of tobacco consumption in the developed world, COPD affects patient's quality of life, utilization of healthcare resources, and also has adverse economic impacts on the patient and society. At present, more than 16 million adults have COPD in the US and 52 million worldwide, and the disease accounts for approximately 125 500 deaths in the US and 2.74 million globally annually.[3,4] The prevalence of COPD has continued to increase internationally because of rapidly increasing smoking rates in developing nations. By the year 2020, COPD is predicted to become the fifth leading cause of death and disability worldwide.[5] Acute deterioration of chronic symptoms frequently occurs and besides being an essen-

tial part of the natural history, is a common cause of medical visits, hospital admissions and death in COPD.[6] We reviewed published literature on the etiology, pathophysiology, treatment and outcome of acute exacerbations of COPD (AECOPD) by searching MEDLINE, EMBASE, and CINAHL® databases. The following search terms were used: acute exacerbation of COPD, COPD exacerbation, AECOPD, acute exacerbation of chronic bronchitis and AECB. The search encompassed all publications from 1966 until 31 December 2004. Additionally, consensus statements, review articles, and articles written by selected authorities were reviewed.

1. Definition of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)

AECOPD lacks a uniform and widely accepted definition in the published literature. Worsening of one or more chronic symptoms

including dyspnea, cough, sputum production, or sputum purulence appears to be the most commonly accepted definition.[7] Currently, the clinical practice guidelines have incorporated Winnipeg criteria (increased dyspnea, increased sputum volumes and increased sputum purulence) to define and grade the severity of AECOPD (table I). Anthonisen et al.[8] showed that the presence of two or more of these clinical features predicted benefit of antimicrobial therapy in AECOPD. An American-European working group proposed a widely accepted definition of AECOPD as follows: "A sustained worsening of the patients' condition, from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication in a patient with underlying COPD."[9]

2. Role of Bacteria in AECOPD

2.1 Pathogens in AECOPD

At least 80% of AECOPD are caused by infections, although other causes including environmental factors (air pollution, cold air, allergens) may be responsible.[10] The common etiologic organisms are bacteria (40–50%), viruses (30–50%) and atypical bacteria (5–10%). Interestingly, more than one infectious agent is the culprit in 10–20% of all exacerbations.[11-13]

The role of viruses in AECOPD was previously examined with serial serology and viral cultures but more recent studies have utilized polymerase chain reaction (PCR) techniques. The specific viruses and proportion of exacerbations caused by each of these are detailed in table II. Soler et al.[11] analyzed serologic samples for viruses in 38 of 50 patients with exacerbations of COPD that required intensive care admission. Viruses were isolated in six (15.8%) of the cases, influenza virus in five and respiratory syncytial virus in one exacerbation. In three of the five influenza infections, a concomitant bacterial pathogen was also present. More recent data have demonstrated the increasing role of respiratory viruses in AECOPD. Seemungal et al.[20] observed that 64% of all exacerbations were preceded by a cold. In an East London COPD study, 83 patients developed 168 exacerbations.[20] Viruses were detected by reverse transcriptase PCR, viral culture of nasal aspirates and serology in 66 (39.2%) exacerbations. The role of viruses in COPD exacerbations is becoming clearer: viruses cause more severe exacerbations, increase airway obstruction, slow symptom resolution and induce systemic and airway inflammation.[14,20] Rhinoviruses were detected in 39.2% of 168 exacerbations; viral infections caused higher symptom scores and increased levels of inflammatory markers (plasma fibrinogen and interleukin-6). In addition, more severe and frequent exacerbations

Table I. Classification of acute exacerbations of chronic obstructive pulmonary disease (Winnipeg criteria)

Type	Characteristics
I	Increased dyspnea, increased sputum volume, and increased sputum purulence (all three symptoms present)
II	Two of the above three symptoms present
III	One of the above symptoms present plus at least one of the following: upper respiratory tract infection in the last 5 days, fever, increased wheezing, and increased cough

were considered to be a consequence of infection with respiratory viruses.[21]

Atypical bacteria are difficult to isolate but the investigators have performed serologic testing to evaluate the role of chlamydia and mycoplasma in AECOPD. Although mycoplasma infection as a cause of exacerbation is uncommon, *Chlamydia pneumoniae* infection is reported to account for 5–10% of exacerbations, although a concomitant bacterial pathogen may also be present.[15]

The predominant pathogens and their relative frequency in AECOPD are listed in table II. Approximately half of the exacerbations yield positive sputum cultures for aerobic bacteria. Fagon et al.[16] performed bronchoscopy with protected specimen brush before empiric antimicrobial therapy in 54 patients requiring mechanical ventilation for respiratory failure due to AECOPD. The findings were similar to that of sputum culture and showed that *Haemophilus parainfluenzae* was the most common pathogen (11 of 44 organisms), followed by *Streptococcus pneumoniae* (7 of 44), non-typeable *H. influenzae* (6 of 44), and *Moraxella catarrhalis* (3 of 44). A variety of other Gram-negative (8 of 44) and Gram-positive (9 of 44) bacteria were also isolated.

Monso et al.[17] performed bronchoscopies and protected specimen brush cultures in a group of 40 patients with moderately severe stable COPD and in 29 patients who were experiencing an acute exacerbation. In the stable group, 25% of protected specimen brush cultures isolated bacterial pathogens ($>10^3$ cfu/mL) compared with 51.7% of culture-positive samples in the exacerbation group. Non-typeable *H. influenzae* was the most common bacterial pathogen in both groups. Soler et al.[11] also demonstrated positive cultures in bronchoscopic samples during an acute exacerbation. Interestingly, a remarkably high incidence of *Pseudomonas aeruginosa* and other Gram-negative bacilli (14 of 50 patients) was evident in this study. Colonization and infection with Gram-negative organisms including *P. aeruginosa* occurred in patients who had repeated courses of antimicrobial therapy, as is often the case in bronchiectasis.[18] The consistent results of these studies prove that the bacteria are recovered in the distal airways of COPD patients during exacerbations and may be responsible for the observed clinical symptoms.

In the literature there exists criticism of data incriminating bacteria as causative agents of AECOPD. In support, Hirschmann[19,22] eloquently debated that current evidence does not substantiate the role of bacteria because: (i) bacterial colonization is not prevalent during exacerbations, and available pathologic and serologic data fail to demonstrate activation of host defense response; and (ii) antimicrobial trials in AECOPD do not validate advantage, and symptomatic improvement does not coincide with the eradication of bacteria. While more data are definitely needed to further elucidate the pathogenesis of AECOPD, and the role of bacteria and antimicrobials, the evidence reviewed in this paper definitely establishes the importance of bacteria and the use of antimicrobials in patients presenting with two or more symptoms of AECOPD.

2.2 Colonization versus Infection

The role of infection in AECOPD has been controversial for a long time, although the antimicrobials are prescribed frequently to treat these patients. Early investigators identified increased num-

Table II. Pathogens associated with acute exacerbations of COPD[11-19]

Frequency of exacerbations (%)	Specific organism	Proportion of pathogens (%)
Viruses		
30–50	Influenza A and B	30–40
	Parainfluenzae 1,2, and 3	20–30
	Rhinovirus	15–25
	Coronavirus	10–20
	Adenovirus	5–10
	Respiratory syncytial virus	10–15
Atypical bacteria		
5–10	*Chlamydia pneumoniae*	90–95
	Mycoplasma pneumoniae	5–10
Bacteria		
40–50	Non-typeable *Haemophilus influenzae*	40–60
	Streptococcus pneumoniae	15–30
	Moraxella catarrhalis	15–30
	H. parainfluenzae	Isolated frequently but pathogenetic significance unknown
	Pseudomonas aeruginosa and Enterobacteriaceae (*Escherichia coli, Klebsiella pneumoniae* or *K. oxytoca*)	Isolated in severe COPD with recurrent exacerbations. Possible underlying bronchiectasis

ber of bacteria and neutrophils in the sputum during exacerbations.[18,23,24] Bacteria were thought not only to be the primary cause of the exacerbations but were also considered to be the secondary invaders following acute viral or mycoplasma infection. Patel et al.[25] recently demonstrated that lower airway colonization in the stable state was associated with increased exacerbation frequency and colonization. Furthermore, non-typeable *H. influenzae* colonization led to higher total symptom score and sputum purulence. However, evaluating the role of bacterial infection in AECOPD has been a difficult task for a variety of reasons. Because the airways of many stable patients with COPD are colonized by *H. influenzae, S. pneumoniae* and *M. catarrhalis*, evaluation of the expectorated sputum during exacerbations may be inconclusive. Serologic studies attempted to establish a causal relationship between bacterial infection and acute exacerbation by finding an acute antibody response in serum to these bacteria.[26] These studies had conflicting results and, in general, failed to establish a correlation between the antibody titers and exacerbations.[27] Most studies used the whole organism preparations of unrelated strains as the antigen for serologic studies, and therefore measured a mixture of antibodies to a combination of antigens.[26-28] Future studies may utilize antibody response to more specific surface antigens of bacteria to establish the importance of bacterial infection in COPD.

2.3 Sputum Color as a Guide to Therapy

Positive sputum culture does not predict benefit of antimicrobial therapy in AECOPD.[17] Increased sputum purulence was previously thought to be associated with bacterial exacerbations.[29] Airway infection rather than colonization activate secondary host defenses and recruit neutrophils to the airways.[30] Therefore, an acute exacerbation will be associated with change of sputum color from mucoid to purulent (myeloperoxidase from neutrophil azurophil granules is green colored), which will reverse on resolution.[30] Stockley et al.[31] studied sputum characteristics in 121 COPD patients presenting with an acute exacerbation. A positive bacterial culture was obtained from 84% of patients who expectorated green, purulent sputum. White or clear sputum yielded a positive bacterial culture in only 38% of exacerbations. In contrast, on repeat sputum culture in stable state, the incidence of positive bacterial culture was similar (38% and 41%, respectively) with purulent and mucoid sputum. Furthermore, all exacerbations associated with mucoid sputum improved without antimicrobials. This study provides additional evidence that bacteria play an important role in causing acute exacerbations and that antimicrobial success can be predicted simply by recognizing sputum color.

Table III. Relative risk of an exacerbation according to whether a new bacterial pathogen or a strain of bacterial pathogen was isolated (reproduced from Sethi et al.,[32] with permission)

Pathogen	Frequency of exacerbation					
	No. of exacerbations/ total no. of visits (%)		Relative risk (95% CI)a	No. of exacerbations/ total no. of visits (%)		Relative risk (95% CI)a
	pathogen (%)	no pathogen (%)		new strain (%)	no new strain (%)	
Any pathogen	23.6	18.0	1.44 (1.24, 1.68	33.0	15.4	2.15 (1.83, 2.53)
Haemophilus influenzae	20.5	19.7	1.14 (0.94, 1.38)	26.2	17.1	1.69 (1.37, 2.09)
Moraxella catarrhalis	34.6	18.7	1.99 (1.52, 2.62)	48.8	16.6	2.96 (2.39, 3.67
Streptococcus pneumoniae	25.0	19.7	1.40 (1.05, 1.87)	32.0	18.0	1.77 (1.14, 2.75)

a   Relative risk of an exacerbation is the presence of a new pathogen or a new strain compared with its absence.

2.4 A New Strain of Old Bacteria

Sethi et al.[32] recently published data strongly supporting the bacterial etiology of some exacerbations (table III). They cultured sputum samples for pathogenic bacteria on a monthly basis in COPD patients during stable state as well as during exacerbations and typed the strains of bacteria using molecular methods. About 48% of exacerbations were associated with positive sputum cultures. About 48% of exacerbations were associated with positive sputum cultures. A bacterial pathogen was isolated in 23.6% of exacerbations compared with 18% with no pathogen (p < 0.001). Interestingly, a new bacterial strain was isolated in 33% of exacerbations compared with 15.4% of exacerbations in which no new strains were identified (p < 0.001). In particular, acquiring a new strain of *H. influenzae, S. pneumoniae*, and *M. catarrhalis* correlated with a significantly higher rate of acute exacerbations, therefore providing credibility to the concept that bacteria play a causative role in AECOPD.
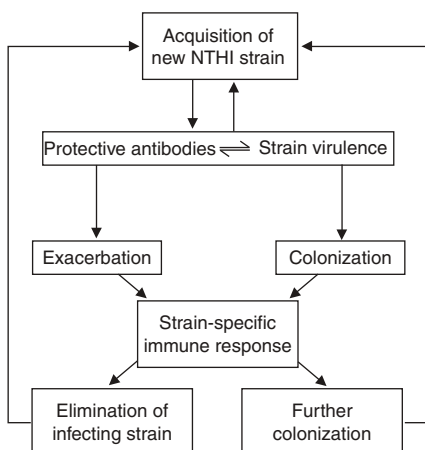
Fig. 1. Model of recurrent infection by non-typeable *Haemophilus influenzae* (NTHI) in patients with COPD (reproduced from Sethi,[33] with permission).

2.5 Model of Recurrent Infection

Data published by Sethi[33] lend credence to their previously advanced model of recurrent bacterial infections, where virulence of the infecting organism and the strain-specific immune response appear to be important determinants of acute exacerbation. Acquisition of a new strain of organism by a patient who possesses pre-existing protective antibodies will lead to no increase in symptoms and hence colonization. The absence of defending antibodies to the newly acquired bacterial strain will cause an exacerbation. Development of antibodies to the infecting bacteria will help clear the organism. Recurrent infections from antigenically different virulent strains in repetitive fashion are an attractive model of pathogenesis of AECOPD (figure 1).[32]

3. Trials of Antimicrobial Therapy in AECOPD

The role of bacterial infection in AECOPD can also be assessed by systematically evaluating the efficacy of antimicrobial therapy. Anthonisen et al.[8] helped settle the controversy over the roles of bacterial infection and antimicrobials in AECOPD. Over a 3-year period, 173 patients with COPD developed 362 exacerbations; 180 exacerbations were treated with placebo and 182 with antimicrobial therapy. The exacerbations were classified according to the Winnipeg criteria based on symptoms of increased dyspnea, increased sputum volume, and increased sputum purulence. A type I exacerbation was defined when all three symptoms were present, type II when two symptoms were present and type III when there was only one symptom (table I). Therapeutic success was defined as 'resolution' if all symptoms returned to baseline within 21 days, 'no resolution' if all symptoms did not resolve and 'failure with deterioration' when symptoms worsened. Considering all exacerbations, treatment with antimicrobials led to higher resolution (68.1%) compared with placebo (55%, p < 0.05) [figure 2]. Deterioration occurred in 9.9% of those treated with antimicrobials, compared with 18.9% with placebo (figure 3). The rate of peak

flow recovery was faster with antimicrobial treatment compared with placebo. Analysis according to the *a priori* subgroups showed that the exacerbations classified as type I achieved the greatest success with antimicrobial therapy (62.9% vs 43% with placebo, $p < 0.05$). In type II exacerbations, the antimicrobials were still associated with better outcome than placebo, whereas the success with antimicrobial therapy was not significantly better than placebo in type III exacerbations. Correspondingly, deterioration occurred less frequently on antimicrobial therapy in patients categorized as type I or type II exacerbations. Overall, the length of illness was 2 days shorter for the antimicrobial-treated group compared with the placebo-treated group.

A meta-analysis by Saint et al.[34] reviewed nine randomized controlled trials published from 1955 through to 1994. The outcome data were retrieved from each of the studies and transformed into units of standard deviation, and the effect size was calculated. The overall effect size was 0.22 (95% CI 0.10, 0.34), thus, establishing a benefit with antimicrobial therapy compared with placebo. The mean change in PEFR favored the antimicrobial-treated group by a difference of 10.75 L/min (95% CI 4.96, 16.54, $p < 0.05$). The meta-analysis also demonstrated that the studies that included a large number of patients and also inpatients displayed a greater benefit from antimicrobial therapy, possibly because these exacerbations were more severe. Discrepancies in outcome in these studies were possibly secondary to design flaws, small numbers of patients, unclear selection criteria, non-standard evaluation criteria and lack of patient stratification.[34-36] Patients with different severities of COPD have exacerbations with diverse organisms; therefore, further studies should be conducted to assess different classes of antimicrobials in specific clinical situations. In patients with more severe air flow obstruction, the bacteriology shifted from *Pneumococcus* spp. and *Haemophilus* spp. to more
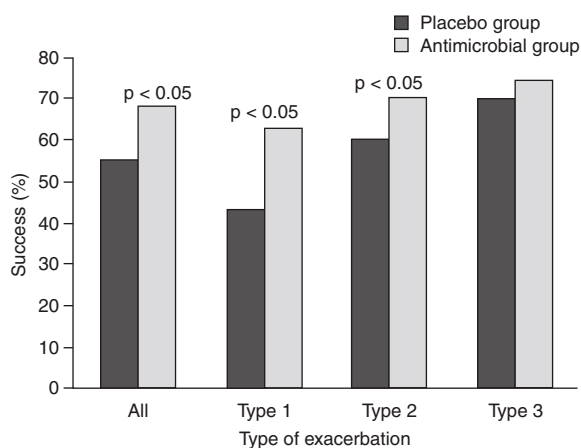

Fig. 3. Rate of failure with deterioration while taking antimicrobials or placebo in acute exacerbations of COPD stratified according to the type of exacerbation (reproduced from Anthonisen et al.,[8] with permission).
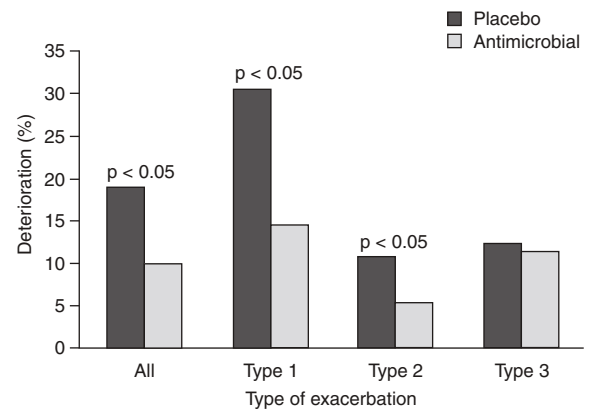
complex organisms such as Enterobacteriaceae and *Pseudomonas* spp. Similarly Miravitlles et al.[37] found that *H. influenzae* and *P. aeruginosa* were more common in patients with FEV_1 values of <50% of predicted. These studies further corroborate that patients with poor lung function tended to have more frequent exacerbations, and received repeated antimicrobial therapy that likely led to alteration of the airway microbial flora.

4. AECOPD and Natural History of COPD

4.1 Vicious Circle Hypothesis

It has been suggested that the progressive deterioration of lung function in patients with COPD is produced by bacterial colonization of the lower respiratory tract and recurrent infective exacerbations. Airway colonization in low numbers may not engender an inflammatory response.[29] As bacterial counts increase, neutrophilic host response leads to release of pro-inflammatory cytokines, and activated proteinases. Wilkinson et al.[38] have recently shown that increase in airway bacterial load and change in the colonizing bacterial type contributed to greater airway inflammation and accelerated decline in FEV_1. In 30 stable COPD patients, the relationship between absolute FEV_1 and change in bacterial load was statistically significant ($r = 0.593$, $p < 0.001$). Stockley et al.[39] recently confirmed that purulent sputum correlated directly with the myeloperoxidase content of sputum and with various other indicators of airway inflammation. Visual measurements of sputum color correlated strongly with myeloperoxidase, interleukin-8, leukocyte elastase (both activity and total quantity), sputum volume, protein leak, and secretory leukocyte proteinase inhibitor. This study provides a useful scientific tool for improving the monitoring of chronic airways diseases and response to treatment. Inflammatory cytokines along with bacterial products im-

Fig. 2. Rate of successful response to antimicrobials or placebo in acute exacerbations of COPD stratified according to the type of exacerbation (reproduced from Anthonisen et al.,[8] with permission).

pair mucociliary function, mucus gland hyperplasia, mucus hyper-secretion, and tissue damage, particularly of the small airways and the alveoli, leading to airflow obstruction. Bacterial colonization is relatively common in stable COPD patients. Acquisition of a new bacterial pathogen or a newer strain of the colonizing bacteria allows proliferation of organisms and an increase in the bacterial load. The higher bacterial load facilitates neutrophilic influx and inflammatory response ensues.[31,38-40]

Therefore, a self-perpetuating vicious circle of host- and bacteria-mediated respiratory tract damage sets in. Sustained by products of inflammation, this cycle impairs host defense response and predisposes to further bacterial colonization and infections. This process has been termed the 'vicious circle hypothesis' and is likely responsible for progressive deterioration of lung function (figure 4).[41]

4.2 Progression of COPD following AECOPD

Whether the acute exacerbations lead to decline in lung function or contribute to the progression of COPD has been more clearly elucidated in recent studies. The early studies of Fletcher,[43] Howard,[44] and Bates[45] demonstrated that acute respiratory illnesses did not contribute to the progression of airway obstruction over the long-term. However, more recent studies have ob-
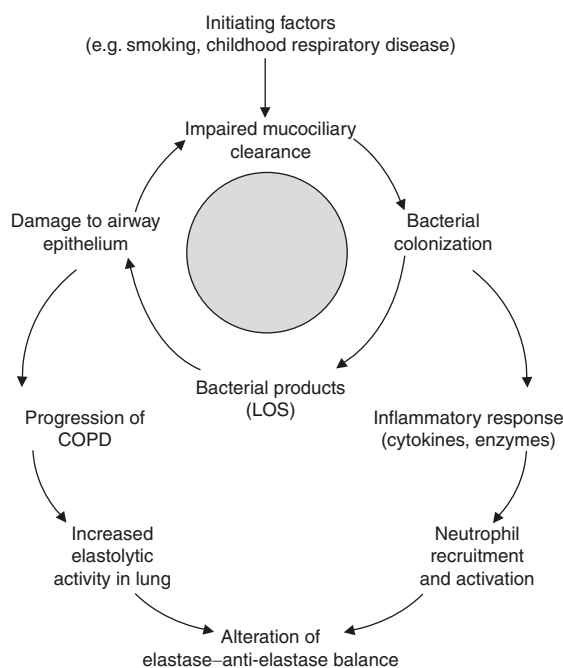
tained different results. Lung Health Study data were analyzed to assess the influence of respiratory illnesses on the rate of decline of FEV_1, over the 5-year study duration.[46] Acute respiratory illnesses were associated with an excessive decline in lung function proportional to the exacerbation frequency among individuals who continued to smoke, as opposed to no deterioration in individuals who ceased smoking. Kanner et al.,[47] who demonstrated that frequent respiratory tract infections in patients with COPD led to a more rapid decline in lung function, supported this hypothesis. Recently, Seemungal et al.[48] prospectively measured PEF in COPD patients before, during, and after acute outpatient exacerbations. Incomplete recovery of lung function was noted in 25% of patients at 35 days, and 7% of patients had not returned to baseline lung function at 3 months. These studies support the hypothesis that repeated acute exacerbations are a factor in progressive airways obstruction and likely affect the natural history of COPD.[46-49]

4.3 Predictors of Poor Outcome from an Exacerbation

Acute exacerbations are a common cause of hospitalization and death in patients with COPD. The previously reported mortality rates of 20–40%[50] have now decreased to 11%, as recently reported by Connors et al.[51] However, these patients continue to have poor long-term prognosis, as a mortality rate of 43% at 1 year and 49% at 2 years was reported. The predictors of high long-term mortality have been identified as follows: severity of physiologic abnormalities during exacerbation, poor overall health status, comorbidities, poor nutrition as indicated by low body mass index, and low serum albumin.

In 1995, Ball et al.[52] found that the presence of cardiovascular comorbidity and more than four exacerbations in the previous year were associated with treatment failure. In a retrospective study of 232 exacerbations in 107 patients with COPD, Dewan et al.[53] identified patient host factors and not the antimicrobial choice as influencing treatment outcome. The use of home oxygen and frequency of exacerbation correctly classified treatment failure in 83% of the patients. The presence of cardiovascular comorbidity combined with greater than four exacerbations in the previous year has a sensitivity of 70% and specificity of 37% in predicting treatment failure.[52,54] In other studies, advanced age, significant impairment of lung function, poor performance status, comorbid conditions and a history of previous frequent exacerbations requiring systemic corticosteroids characterized the high-risk group.[42,55] Additionally, the risk factors for relapse are increasing number of previous exacerbations, severity of airflow obstruction, and increasing baseline dyspnea.[56]

Fig. 4. Schematic diagram detailing the 'vicious circle hypothesis'. The changes in the host defense mechanisms predispose to the repeated bacterial infections. This establishes a self-perpetuating vicious circle of respiratory tract damage and progression of disease.[41,42] **LOS** = lipo-oligosaccharides.

5. Costs of AECOPD

AECOPD are associated with a significant increase in health-care utilization and are a frequent cause of hospital admission.[57-60] Therefore, exacerbations are the major cost drivers in overall cost of COPD, which consumes significant healthcare resources.[61,62] Several investigators estimated the cost of acute exacerbation in patients above the age of 65 years to be $US1.2 billion, and $US419 million for patients below this age.[61] The annual costs of AECOPD in England and Wales were estimated to be £45 million by McGuire et al.;[63] this represents 0.1% and 0.2% of the National Health Services budget, respectively. Data from France demonstrated that direct healthcare costs per acute exacerbation were about FF3289, of which 60% were hospital related.[64] In a recent Swedish study, the average healthcare costs per exacerbation were SEK120, SEK354, SEK2111 and SEK21852 for mild, mild/moderate, moderate and severe exacerbations, respectively.[65] These translated to SEK1.7 billion per year nationally where hospitalization was the key cost driver, accounting for 67% of the total cost. AECOPD is costly; the costs are variable but higher for severe exacerbations and in patients requiring hospitalization. A retrospective study by Destache et al.[66] reported reduced overall healthcare costs with the use of newer agents compared with first-line antimicrobials. Another such study by Torrance et al.[67] demonstrated benefit and lower total costs with fluoroquinolones in patients who had a history of moderate-to-severe bronchitis and at least four exacerbations in the previous year.

Several recent studies have supported the use of different antimicrobials based on patient stratification.[68-71] These studies utilized either computerized modeling or a prospective study design. The use of newer broad-spectrum antimicrobials was associated with better clinical outcomes and lower healthcare costs in patients with AECOPD who had moderate-to-severe exacerbations and comorbid conditions. Outpatient drug costs, an important component of total AECOPD expenditure, vary inversely with severity of exacerbation. Van Barlingen et al.[71] reported lower drug utilization costs in severe (7%) compared with mild (17%) exacerbations.

Current antimicrobial trials in AECOPD are focusing on symptomatic improvement as the outcome measure.[8,34,35,43,50-52,55] Since exacerbations frequently recur, a disease-free interval (DFI) may be more meaningful. DFI is defined as "the length of time in days between the end of therapy and the beginning of next episode".[72] An antimicrobial agent successful in eradicating bacterial colonization from the lower airways will delay the recurrence.[73] DFI is an outcome measure that should be evaluated additionally in future clinical trials, to demonstrate clinical success of antimicrobial therapy.

6. Risk Stratification and Treatment Guidelines

Treatment failures in AECOPD lead to return physician or clinic visits, require repeated courses of antimicrobial therapy, risk hospitalization, and increase overall costs.[74] Furthermore, patients with severe COPD have limited ventilatory reserve, and acute exacerbations are a common cause of acute respiratory failure requiring intubation and mechanical ventilation.[75] Stratification of patients into risk categories may allow physicians to select appropriate antimicrobial therapy, so as to avoid treatment failure and improve outcome in an era of increasing antimicrobial resistance.[74-78]

6.1 Previous Risk Stratification Schemes

Several risk stratification schemes have been proposed to improve initial microbial selection. Lode[75] in 1991 proposed that patients be divided into three groups based on severity of lung function, number of exacerbations each year, and presence of a comorbidity. Treatment with oral amoxicillin, doxycycline, trimethoprim/sulfamethoxazole (co-trimoxazole) or a macrolide was recommended for low-risk patients (first degree). Patients with a longer history of COPD, several exacerbations each year, other comorbidity, impaired lung function and inpatients were considered high-risk patients (second and third degree).

In 1994, Balter et al.[79] initially suggested a five-group classification of patients with AECOPD, and in a recent publication these patient are classified into four groups.[80] The patients with acute simple bronchitis and no previous respiratory problems were classified as Group 0, the Group I patients had simple chronic bronchitis with minimal or no impairment of pulmonary function and without any risk factors. Group II patients were similar to Group I but had one or more significant comorbid illnesses such as congestive heart failure, diabetes mellitus, chronic renal failure or chronic liver disease. Group III patients were classified as having chronic bronchial sepsis. This scheme is problematic and impractical for various reasons, as Group 0 patients do not have COPD and Group III patients are those who have bronchiectasis or are frequently colonized by Gram-negative bacterial pathogens, which may not be the causative pathogen. In the older classification, the division between Group 3 and Group 4 was arbitrary and the treatment recommendations were identical.[79]

6.2 A Practical Approach

Modified from the publications of Wilson,[42] Grossman[81] and Balter et al.[79,80] we proposed a simpler risk scheme to stratify AECOPD (table IV).[82] It may be more practical to categorize all patients with Anthonisen's type I and type II exacerbations into either simple or complicated AECOPD.[83] Since antimicrobial

Table IV. Risk stratification of patients with acute exacerbations of chronic obstructive pulmonary disease[82]

Classification	Characteristics
Simple chronic bronchitis	Patients with chronic bronchitis and two or more of the following symptoms (Anthonisen's type I and II): increased cough; increased sputum volume; increased dyspnea
Complicated chronic bronchitis	Patients with chronic bronchitis and Anthonisen's type I and II exacerbations and at least one of the following risk factors: FEV$_1$ <50% predicted; experience more than four exacerbations/year; comorbid medical illness (congestive heart failure, diabetes mellitus, chronic renal failure, or chronic liver disease)

therapy has not been shown to benefit type III exacerbation, therefore, symptomatic therapy suffices for these patients. Patients with simple AECOPD will have only mild-to-moderate impairment of lung function (FEV$_1$ >50% predicted), have fewer than four exacerbations per year and are likely to be colonized with usual strains of *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*, although viral infections often precede bacterial superinfection. Recommendations are to use any first-line antimicrobial agent, as the consequences of treatment failure are not likely to be grave. The patients with complicated AECOPD have poorer underlying lung function (FEV$_1$ <50% predicted), significant medical comorbidity (e.g. diabetes, congestive heart failure, chronic renal disease, chronic liver disease) and/or experience four or more exacerbations per year. The predominant organisms may not be more likely to be resistant strains of *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*, but since treatment failure may have major implications, empiric antimicrobial therapy directed toward resistant organisms should be initiated. Second-line antimicrobial agents such as quinolones, amoxicillin/clavulanic acid, second- or third-generation cephalosporins or second-generation macrolides are recommended in these patients. Occasional patients with repetitive exacerbations are likely to become colonized with *P. aeruginosa*; some of these individuals have underlying bronchiectasis when studied by high-resolution imaging studies. Since many of these patients have received multiple courses of antimicrobials, the presence of *P. aeruginosa* represents colonization. In unusual circumstances when infection is documented, use of a quinolone with antipseudomonal activity empirically and further tailoring the therapy based on sputum culture is appropriate. Although none of these proposed classification schemes have been prospectively tested for their utility and efficacy, they emphasize that potentially resistant organisms should be targeted in patients at high risk of antimicrobial treatment failure.

7. Antimicrobial Agents and Resistance Patterns

First-line antimicrobials demonstrated equivalent efficacy in the study by Anthonisen et al.[8] Since then an array of newer antimicrobial agents have become available. These agents have generally been as successful in treating AECOPD as previously approved antimicrobials. Whether one antimicrobial agent is superior to another is not known, because the trials have not been designed with this goal in mind. A retrospective study by Adams et al.[84] looked at the risk factors for treatment failure at 14 days after onset of AECOPD. A return visit within 14 days with persistent or worsening symptoms was defined as treatment failure. The failure rates were reported to be 54% with amoxicillin, 8% with amoxicillin/clavulanic acid, 11% with trimethoprim/sulfamethoxazole, and 21% with macrolides. Another retrospective study by Destache et al.[66] analyzed 224 episodes of AECOPD requiring antimicrobials in 60 outpatients. The antimicrobials were divided into three groups: first-line (amoxicillin, trimethoprim/sulfamethoxazole, tetracycline, erythromycin), second-line (cefuroxime, cefaclor, cefprozil), and third-line (amoxicillin/clavulanic acid, azithromycin, ciprofloxacin). Deterioration of symptoms requiring additional antimicrobials within 2 weeks of initial therapy was defined as treatment failure. The patients who received first-line agents had significantly higher failure rates; the patients treated with third-line agents were hospitalized less frequently, and had a longer exacerbation-free interval.

In 1974, <5% of isolates of *H. influenzae* were β-lactamase positive in the US.[23] Since then, resistance to the commonly used antimicrobials among non-typeable *H. influenzae*, *S. pneumoniae* and *M. catarrhalis* has dramatically risen over the past 2 decades. In 1997, the prevalence of β-lactamase producing *H. influenzae* exceeded 33%,[85] and presently 30% of all *H. influenzae* strains are estimated to be β-lactamase positive.[74,85,86] Furthermore, 35% of *H. influenzae* strains are known to possess multiple mechanisms of antimicrobial resistance, including production of β-lactamase and alterations in penicillin binding. Additionally, 15% or more *H. influenzae* are cefaclor- and cefprozil-resistant, and 3% are azithromycin-resistant.[85] The prevalence of penicillin-resistant *S. pneumoniae* isolates increased from 3–6% before 1991 to 43.8% in 1997.[82] The current data on resistance are similar:[85-88] a survey of 33 medical centers from November 1999 to April 2000 showed that approximately 35% of *S. pneumoniae* are resistant to penicillin, with 60% of isolates exhibiting a high level of resistance (minimum inhibitory concentration ≥2 μg/mL).[88] Bronchopulmonary infections comprised 44.5% and 22.1% of resistant infections with *S. pneumoniae* were from patients ≥65 years of age. The current overall pneumococcal resistance prevalence in the US is: macrolides 25.9%, clindamycin 8.8%, tetracy-

cline 16.4%, chloramphenicol 8.4%, and trimethoprim/sulfamethoxazole 30.3%.[87,88] In another study, a total of 6515 isolates of *S. pneumoniae* and 6726 *H. influenzae* strains revealed ampicillin resistance of approximately 25% among *H. influenzae* isolates and did not significantly differ between strains from community-acquired infections or hospitalized patients.[8] Furthermore, β-lactamase-negative ampicillin-resistant strains and fluoroquinolone-refractory strains were rare (0.3% and ≤0.2%, respectively). Macrolide-resistance to *H. influenzae* was 24.4% (clarithromycin) in hospitalized patients with pneumonia. Another recent study from North America demonstrated nonsusceptibility rates to penicillin at 21.0%, cefotaxime 7.3%, imipenem 3.8%, ciprofloxacin 11.2%, erythromycin 30.3%, and tetracycline 38.5%.[89]

During 2000–01, Jones et al.[90] prospectively collected 1995 isolates of *H. influenzae*, 1870 isolates of *S. pneumoniae* and 649 isolates of *M. catarrhalis* from hospital laboratories in France, Germany, Greece, Italy, Spain, and the UK. *S. pneumoniae* isolates were 99.6% susceptible to moxifloxacin, gatifloxacin and levofloxacin, and *H. influenzae* and *M. catarrhalis* were 100% susceptible. The incidence of penicillin non-susceptibility to *S. pneumoniae* remained similar to or higher than previously reported: France, 165 of 291 (56.7%); Germany, 46 of 506 (9.1%); Greece, 20 of 55 (36.4%); Italy, 45 of 364 (12.4%); Spain, 146 of 268 (54.5%); and the UK, 26 of 386 (6.7%). The β-lactamase production among *H. influenzae* isolates ranged from 6.2% to 33.1% per country. A higher resistance against *Pneumococcus* has been reported from Spain (53.4%) than in Italy (15.1%), whereas erythromycin resistance was higher in Italy (42.9%) than in Spain (28.6%).[91]

Selective pressure from antimicrobial prescription appears to be the most important factor associated with drug-resistant *S. pneumoniae*. Resistance is encountered more commonly in patients who have identifiable risk factors, including age >65 years, prescription of β-lactam antimicrobials during the past 3 months, previous hospitalizations, and nursing home residence.[86,92]

However, the majority of studies have not classified the exacerbations in detail and have not demonstrated a difference in clinical outcomes with newer or the older antimicrobial agents.[93-95] Grossman et al.[96] assessed safety and efficacy of ciprofloxacin versus standard antimicrobial care in patients with moderate-to-severe bronchitis and at least four exacerbations in the previous year. A trend towards accelerated resolution with ciprofloxacin existed but the difference was not statistically significant in this open-label, uncontrolled study. A retrospective analysis performed by Madaras-Kelly et al.[97] concluded that the use of older versus newer antimicrobials did not independently predict either the outcome or the subsequent development of an exacerbation.

The initial cure rates (93% vs 95%, p = 0.48) and 6-month exacerbation-free period (34% vs 28%, p = 0.37) were similar in patients receiving older versus newer antimicrobials.[97] Therefore, large clinical trials are needed to establish the adequacy of current empiric guidelines and to address the role of newer broad-spectrum antimicrobials.

8. Prescribing the Appropriate Antimicrobial

There are several theoretical characteristics that would be desirable in selecting an antimicrobial for AECOPD: (i) activity against the most common and most likely etiologic organisms, including *H. influenzae*, *S. pneumoniae* and *M. catarrhalis;* (ii) resistance to destruction by β-lactamase; (iii) narrow spectrum of activity against the likely pathogen; (iv) good penetration into the sputum, bronchial mucosa and epithelial lining fluid; (v) easy to take, with few adverse effects; (vi) prolonged DFI or delay of the next exacerbation; (vii) cost effectiveness, including the drug and hospital costs and the costs of treatment failure (table V).[98]

Table V. Antimicrobials used in the treatment of acute exacerbations of chronic obstructive pulmonary disease

First-line antimicrobials
Aminopenicillins
amoxicillin
pivampicillin
bacampicillin
Tetracyclines
tetracycline
doxycycline
minocycline
Trimethoprim/sulfamethoxazole (co-trimoxazole)
Second-line antimicrobials
Second-generation cephalosporins
cefaclor
cefuroxime axetil
Third-generation cephalosporins
cefixime
Amoxicillin/clavulanic acid
Newer macrolides
clarithromycin
azithromycin
Fluoroquinolones
levofloxacin
moxifloxacin
gatifloxacin
gemifloxacin

9. First-Line Antimicrobials

In 1948, chlortetracycline was the first tetracycline discovered. Since then, tetracycline, demeclocycline, doxycycline, and minocycline have been synthesized for clinical use, although doxycycline and minocycline are the most frequently prescribed. The tetracyclines are broad-spectrum bacteriostatic antimicrobials. They either passively diffuse or are actively transported into the bacterial cell. They inhibit ribosomal bacterial protein synthesis. The mechanism of resistance to tetracycline is to prevent accumulation of the drug inside the cell by decreasing influx or increasing efflux. Many of the original trials of antimicrobial therapy demonstrated that tetracycline therapy was more effective than placebo in milder infections. Tetracyclines can be used in AECOPD because they are active against *H. influenzae* and atypical pathogens, but there have been reports of increasing resistance against pneumococci.[88-90,99]

β-Lactam antimicrobials are generally bactericidal by virtue of inhibition of bacterial cell wall synthesis. Bacterial resistance to β-lactams may occur by any of three general mechanisms: (i) decreased penetration of antimicrobial to the target binding protein in the bacterial plasma membrane; (ii) alterations in penicillin-binding proteins; and (iii) production of β-lactamase, which may cleave the penicillins or cephalosporins. Production of β-lactamase is the most important mechanism. The bacteria may either synthesize β-lactamase constitutively or initiate synthesis in the presence of antimicrobials; the β-lactamase positivity varies between centers and countries. Amoxicillin has been widely used for the management of AECOPD.[74] In countries and centers where resistance among *H. influenzae* and pneumococci remain at low levels, β-lactam antimicrobials are drugs of choice in patients with purulent or type I and II exacerbations. Despite their relatively poor activity and suboptimal respiratory pharmacokinetics, cephalexin and cefaclor have been extensively used for the management of AECOPD. The newer cephalosporins, cefprozil and cefixime, may have some advantages such as activity against resistant pneumococci, but have not been proven to be superior to amoxicillin[100,101] when organisms are fully sensitive to both agents.

The combination of amoxicillin/clavulanic acid is an improvement over amoxicillin alone when prescribed for β-lactamase-producing organisms. Addition of clavulanic acid makes the combination therapy resistant to most but not all bacterial β-lactamases. Most studies of patients with lower respiratory tract infection have shown this agent to be equivalent to standard comparators.[102] Comparison with cefixime and ciprofloxacin showed better clinical success in AECOPD but no significant difference in bacterial eradication rates.[103]

Trimethoprim/sulfamethoxazole, combined in a ratio of 1 : 20, is a bactericidal combination which works synergistically against bacterial organisms. Both antimicrobials inhibit enzyme systems involved in the bacterial synthesis of tetrahydrofolic acid by different mechanisms. Resistance occurs with development of a target enzyme with decreased bacterial affinity for the drugs and via dihydrofolic reductase gene mutations. Although very popular in the 1970s and 1980s, the potential for resistance and increasing availability of safer agents has resulted in declining use of this antimicrobial. In older studies, comparisons with oral cephalosporins have generally shown equivalent efficacy.[104] The SENTRY Antimicrobial Surveillance Program reported 15–20% trimethoprim/sulfamethoxazole resistance to common respiratory pathogens in Europe and the US, and higher in Latin America and Asia-Pacific regions.[105] Penicillin-resistant pneumococci have 80–90% likelihood of cross-resistance to trimethoprim/sulfamethoxazole.[106] Consequently, local resistance patterns and severity of disease should be taken into account for appropriate use of trimethoprim/sulfamethoxazole in AECOPD.

10. Second-Line Antimicrobials

The mechanism of antimicrobial action of newer macrolides is similar to that of erythromycin. These agents bind to the 50S subunit of bacterial ribosome and inhibit bacterial protein synthesis. Compared with erythromycin, these agents are more acid stable, have improved oral absorption and tolerance, and have a broader spectrum of antimicrobial activity. Macrolides and fluoroquinolones are active against *C. pneumoniae*. There has been increasing resistance to macrolides among Gram-positive organisms. Up to 15% of *S. pneumoniae* may have resistance to erythromycin and cross-resistance to other macrolides. Azithromycin and clarithromycin have improved pharmacokinetics and antimicrobial activity against *H. influenzae* compared with erythromycin.[84] The significant advantages of azithromycin are enhanced potency against *H. influenzae,* once-daily administration, reduced rates of adverse effects (specifically gastrointestinal effects), an abbreviated 3- to 5-day treatment course, and perhaps a reduced frequency of relapse during extended follow-up.[107-110] The efficacy and safety of a 3-day regimen of azithromycin and of a 10-day regimen of amoxicillin/clavulanic acid were compared in patients with AECOPD. Major improvement or cure on day 14 occurred in 95% of patients in the azithromycin group compared with 90% on amoxicillin/clavulanic acid. At 30 days, the success was 77% and 66% in azithromycin- and amoxicillin/clavulanic acid-treated patients, respectively.[108] Another recent randomized, double-blind, multicenter trial compared the safety and efficacy of oral azithromycin and levofloxacin in outpatients with AECOPD.[110] Both treatments were well tolerated, and favorable

clinical outcomes were demonstrated in 89% of patients receiving azithromycin and 92% of patients receiving levofloxacin by day 4 of therapy. At day 24, favorable responses were approximately 82% and 86% and bacterial eradication rates were 96% and 85%, respectively, for patients in the two treatment groups. Another study compared the clinical efficacy and tolerability of 5-day courses of dirithromycin and azithromycin given once daily for the treatment of AECOPD. Comparable clinical efficacy was revealed between 5-day courses of once-daily dirithromycin and azithromycin in AECOPD.[111]

Clarithromycin *per se* has only intermediate activity against *H. influenzae* but synergy with one of its metabolites increases its activity to satisfactory levels.[109,112] Clinical studies of clarithromycin involving 7- to 14-day regimens in patients with mild-to-moderate infections have shown equivalence to ampicillin.[113] A phase III randomized, double-blind study in AECOPD patients demonstrated that extended release clarithromycin at 500mg once daily compared favorably with immediate release clarithromycin 500mg twice daily: the clinical cure rates were 86% and 85%, respectively.[114] A recent study compared clarithromycin with amoxicillin/clavulanic acid in the treatment of AECOPD. Clinical success was documented in 85% of patients receiving erythromycin and was equivalent to amoxicillin/clavulanic acid, and the inidence of adverse events was similar in the two treatment groups.[115]

Fluoroquinolones, synthetic analogs of the original molecule (nalidixic acid), exert their antimicrobial effect by direct inhibition of bacterial DNA synthesis.[116-118] Two bacterial enzymes – DNA gyrase and topoisomerase IV – have essential roles in DNA replication. Fluoroquinolones bind to each of these enzymes, thus interfering with DNA replication, leading to bacterial cell death. Resistance to fluoroquinolones occurs via mutations in the genes by encoding the subunits of DNA gyrase and topoisomerase IV. Altered permeation mechanisms may contribute to resistance by enhancing cytoplasmic membrane efflux pumps. These agents penetrate well into the respiratory secretions and bronchial mucosa, but the clinical relevance of this is uncertain. The respiratory fluoroquinolones are active against both typical and atypical bacterial pathogens. The fluoroquinolones are highly active against β-lactamase producing *H. influenzae* and *M. catarrhalis*. These antimicrobial agents have 70–95% bioavailability after oral administration, a prolonged half-life (>8–12 hours), low protein binding and renal clearance. Fluoroquinolones are well tolerated, and adverse effects are mild and transient, including rash, dizziness, headache, gastrointestinal disturbance (nausea, vomiting, diarrhea, abdominal pain) and minor hematologic abnormalities.

The efficacy of fluoroquinolones has been established in several randomized trials. A community-based study involving more than 300 primary care physicians compared the efficacy of ciprofloxacin and clarithromycin. Equivalent clinical success (93% vs 90%) and bacteriologic eradication (98% vs 95%) were reported with ciprofloxacin compared with clarithromycin. Despite a relatively high inhibitory concentration against *S. pneumoniae,* ciprofloxacin has demonstrated clinical efficacy similar to amoxicillin, clarithromycin and cefuroxime.[119] Oral levofloxacin 250 or 500mg daily was compared with oral cefuroxime axetil (250mg twice daily) in a randomized, double-blind, multicenter study.[120] The cure rates in the intention-to-treat population were 70% for levofloxacin 250mg, 70% for levofloxacin 500mg and 61% for cefuroxime axetil. Another randomized, double-blind study demonstrated equivalent clinical and bacteriologic success with levofloxacin 500mg once daily for a 5- or 7-day course.[121] A shorter course of gatifloxacin for 5 days was compared with 7-day gatifloxacin therapy and 10-day clarithromycin therapy for acute exacerbation of chronic bronchitis.[122] Similar clinical success rates of >88% were reported compared with comparator antimicrobials. Another open-label noncomparative post-marketing trial of gatifloxacin in the treatment of AECOPD in community-based practice settings was reported recently.[123] Overall cure rates were 95.8% for *H. influenzae*, 98.6% for *S. pneumoniae* and 89.2% for *M. catarrhalis*; the most serious adverse effects were nausea (1.5%), dizziness (1.5%), diarrhea (1.2%), and vomiting (0.9%).[123] Another respiratory fluoroquinolone, moxifloxacin, has been reported to be efficacious in patients with AECOPD.[124-126] These multicenter trials compared oral moxifloxacin 400 mg/day for 5 days with oral clarithromycin 500 mg/day for 10 days or intramuscular ceftriaxone 2g once daily for 7 days or oral amoxicillin/clavulanic acid (three 625mg tablets daily for 7 days). Similar clinical success rates, classified as resolution or improvement of symptoms, occurred with moxifloxacin. A multinational, double-blind study, MOSAIC (Moxifloxacin Oral tablets to Standard oral antibiotic regimen given as first-line therapy in out-patients with Acute Infective exacerbations of Chronic Bronchitis), compared effectiveness of moxifloxacin (400mg once daily for 5 days) and standard therapy (amoxicillin [500mg three times daily for 7 days], clarithromycin [500mg twice daily for 7 days], or cefuroxime-axetil [25mg twice daily for 7 days]). Patients were stratified according to oral and inhaled corticosteroid usage. The primary endpoint was clinical success (sufficient improvement, no alternative antimicrobial therapy required) 7–10 days after therapy. Secondary predefined endpoints were clinical cure (return to pre-exacerbation status), further antimicrobial use, time to next exacerbation and bacteriologic success. In this parallel study, 354 patients received moxifloxacin and 376 patients received standard therapy. In an intention-to-treat (ITT) population, clinical success rates were similar (87.6% for mox-

ifloxacin, 83% for standard therapy, p = 0.02) at 7–10 days after therapy. Moxifloxacin showed superior clinical cure rates over standard therapy in both ITT patients (95% CI 1.4, 14.9) and per protocol patients (95% CI 0.3, 15.6), and higher bacteriologic success in microbiologically valid patients (95% CI 0.4, 22.1). Time to next exacerbation was longer with moxifloxacin; median time to new AECOPD was 132.8 days in moxifloxacin, and 118.0 days in standard therapy, respectively (p = 0.03). The occurrence of failure, new exacerbation, or any further antibiotic use was less frequent in moxifloxacin-treated patients for up to 5 months of follow-up (p = 0.03).[127] A recent randomized, double-blind trial of gemifloxacin 320mg once daily antibiotic therapy was used to investigate its efficacy and the magnitude and time course of effect of an AECOPD on health status. Clarithromycin 500mg twice daily for 7 days was used as comparator drug, patients were followed up for 26 weeks. Clinical success rates at the 2–3 week follow-up visit were 85.4% for gemifloxacin and 84.6% for clarithromycin. Bacteriologic success rates were 86.7% for gemifloxacin and 73.1% for clarithromycin. Significantly more patients receiving gemifloxacin than clarithromycin remained free of AECB recurrences (71.0% vs 58.5%, respectively; p = 0.016).[128] The greatest improvement in St George's Respiratory Questionnaire score occurred within the first 4 weeks (mean 8.9 units, 95% CI 6.5, 11.5; p < 0.0001).[128] Subsequently, scores improved more rapidly in patients with no further exacerbations. This study demonstrated sustained effect on health status even after a single episode of AECOPD; recurrences unfavorably affect quality of life. Treatments that reduce exacerbation frequency could have a significant impact on health status. Despite considerable emerging resistance to the other antimicrobial agents, resistance to the newer fluoroquinolones in common respiratory pathogens is a rare occurrence, however, prudent utilization and close surveillance should be maintained.[129]

11. Conclusion

COPD is a major cause of morbidity and mortality. AECOPD are a regularly occurring feature of the natural history of COPD, and antimicrobials have shown effectiveness in the treatment of some of these episodes.[13] Acute exacerbations are the major cause of hospitalizations and physician visits, thus generating the majority of costs involved in caring for COPD patients. Bacterial pathogens responsible for causing AECOPD may play a significant role in the progression of airflow obstruction. In patients with acute bronchitis without underlying lung disease or mild airflow obstruction, the likely etiology is viral infection; antimicrobials should not be prescribed for these patients. Low-risk patients (e.g. simple AECOPD) who meet Winnipeg criteria for type I or II exacerbations (two or three symptoms of increased dyspnea, in-

creased sputum volume, and increased sputum purulence), should be treated. The traditional antimicrobials termed as first-line therapy are appropriate; these include amoxicillin, tetracycline, doxycycline and trimethoprim/sulfamethoxazole. Cure rates with these antimicrobials approach 80–90% in mild-to-moderate exacerbations. In patients who have more severe underlying lung disease, frequent exacerbations, and comorbid conditions, failure of initial antimicrobial therapy may result in repeat visits, hospitalization, and increased morbidity and mortality. In these patients (complicated AECOPD), second-line antimicrobials including macrolides and fluoroquinolones, and second- or third-generation macrolides should be considered.

Clinical trials utilizing newer antimicrobials showed equivalence but not superiority compared with the regimens already in use. Future studies should attempt to identify patients with AECOPD most likely to benefit from antimicrobial therapy. Well defined prospective analyses of cost, DFI, quality-of-life improvement and recovery of lung function should be addressed in these studies to ascertain the utility of antimicrobial therapy in AECOPD.

Acknowledgments

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